REMARKS

This filing is presented in response to the Office Action mailed June 3, 2009.

In the Office Action mailed June 3, 2009, claims 43-49, 51, 120-127, and 129-142 were rejected under 35 USC §112, second paragraph for allegedly being indefinite.

Claims 1-5, 8, 10, 43-49, 51, and 112-142 were rejected for allegedly being obvious under 35 USC §103 based upon Hortin in view of Pittman et al.; Bakker et al.; and Ramabhadran.

In this amendment, clarifications are presented to claims 43, 120, 128, and 136. And, further explanations and evidence are presented in support of the patentability of the pending claims. It is respectfully submitted that all pending claims 1-5, 8, 10, 43-49, 51 and 112-142 are in condition for allowance.

A. Rejection of Claims 43-49, 51, 120-127, and 129-142 Under §112, Second Paragraph has Been Remedied and Should Now be Withdrawn

Claims 43, 120, 128, and 136 have been amended in accordance with the Examiner's helpful suggestions. Specifically, each of these claims has been amended to recite that thrombin generation which is being inhibited, is "in a human" (claims 43, 120 and 128); and that the peptide (claim 136) is for binding to thrombin "in a human."

No new matter is added by any of the amendments to claims 43, 120, 128, and 136. Support is found throughout the present application such as at page 20, lines 27-32; page 21, lines 20-29; and page 21, line 30 to page 22, line 5.

B. Rejection of Claims 1-5, 8, 10, 43-49, 51, and 112-142 Under §103 Should be Withdrawn

In support of this ground of rejection, the Office relied upon arguments appearing on pages 4-8 of the June 3, 2009 Office Action. These arguments were all previously included in the prior Office Action dated December 4, 2008. Applicant traverses those arguments for the reasons and explanations previously provided in the Amendment C filed March 26, 2009.

1. Pittman's Alleged "Explicit Directions"

Several new arguments were presented by the Office in support of the present rejection, and are each addressed individually as follows. Beginning on page 8 of the most recent Action, the Office asserted:

> Applicant alleges that the fact that Pittman indicated that the role of the sulfation sites was not fully understood constitutes a teaching away from the instant invention (Reply, page 31), but the examiner disagrees. Pittman suggested a link between sulfation and Factor V's ability to inhibit thrombin formation; this suggestion represents a clear invitation to experiment and an indication that such a link is possible and even probable. It is not clear how following the explicit direction provided by the prior art constitutes innovation.

In this argument, the Office characterizes Pittman as providing "explicit direction." No. Pittman does not provide "explicit direction." Pittman in fact states that "the precise sites of tyrosine sulfation in factor V remain to be elucidated," p. 6957 of Pittman. Pittman does not provide "explicit directions" that a peptide (or pharmaceutical composition containing such) consisting of an amino acid sequence DYDY or DYDYQ would inhibit thrombin generation. Furthermore, Pittman further explained "at present we do not know if efficient thrombin cleavage of the light chain also requires tyrosine sulfation," p. 6957. In view of this, how can Pittman provide "explicit direction"? The

most that can be gleaned from Pittman are Pittman's speculated guesses as to various sites in factor V for sulfonation. However, speculated guesses in the art are insufficient for supporting an obviousness rejection.

2. Age of References is Relevant

The Office also contended that:

> Applicant's reply suggests that the age of the references somehow disqualifies them from being included in an obviousness rejection (Reply, pages 30-33). Contentions that the reference patents are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See In re Wright, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977).

Page 8 of the June 3, 2009 Office Action.

Contrary to the Office's arguments, the age of a prior art reference is a factor to be considered, particularly in a rapidly advancing and new field, such as that of the present invention. Both the references to Bakker et al. and Ramabhadran are from a different era in this field of art – one from fifteen (15) years ago. If these references are as informative and descriptive of the claims at issue as urged by the Office, then why have the claimed peptides not yet been disclosed in the art? Why has no artisan, prior to the present inventor, identified the claimed peptides as effective thrombin inhibitors?

In point of fact, the present inventor was the first to identify the particular claimed peptides as effective thrombin inhibitors. Neither of the references to Bakker et al. nor Ramabhadran provide any teaching in this regard. In fact, the absence of any relevant teaching in the art after the Bakker et al. and Ramabhadran references, is evidence as to their lack of teaching with regard to the present invention.

3. Bakker's Teaching Away

Further arguments in support of the present rejection by the Office were made as follows:

> Applicant alleges that Bakker teaches away from the invention (Reply, page 32), but it is respectfully submitted that applicant has misinterpreted the teachings of Bakker. The Va_{NO} of Bakker that is discussed in the passage referenced by applicant (page 20665 of Bakker and page 24 of the reply) is not a peptide that consists of the last 27 amino acids of Factor Va, but rather a peptide that includes the entire sequence of Factor Va except for these last 27 amino acids. "[T]he heavy chain of factor Va_{NO} had a slightly increased electrophoretic mobility, indicating the loss of a small peptide ... from the heavy chain" (page 20663, column 2, third full paragraph). Bakker teaches that when the C-terminal 27 amino acids are removed from Factor Va, the resulting peptide (Va_{NO}) activates thrombin more effectively than does native Factor Va; the reply appears to stipulate to the fact that Va_{NO} is a less effective thrombin inhibitor than is Factor Va. The skilled artisan would have concluded from these teachings that these C-terminal 27 amino acids possess an activity that inhibits thrombin activation. This C-terminal portion would therefore have been a region of interest to artisans seeking thrombin inhibitors. The fact that Bakker was not concerned with the exact problem that the instant application addresses does not constitute a teaching away. Patents are relevant as prior art for all they contain. A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art. See M.P.E.P. §2123.

Pages 8-9 of the June 3, 2009 Action.

It is respectfully submitted that the Office does not appreciate Applicant's previous explanations concerning Bakker and the subject matter of the pending claims. First, Applicant is not contending that Bakker describes a peptide that consists of the last 27 amino acids of Factor Va. Instead, Bakker describes a modified factor that lacked this sequence of amino acids. The Office is respectfully referred to pages 31-32 and 45-47 of Applicant's previously submitted Amendment C dated March 26, 2009. Apparently, the Office and Applicant are in agreement that the modified factor Va_{NO} does not contain the noted 27 amino acid peptide.

For ease and convenience in review, Applicant summarizes Bakker's work as follows:

- Bakker investigated certain functional properties of factor Va by forming a modified factor Va_{NO} and then comparing Va to Va_{NO}.
- Va_{NO} was obtained by incubating factor Va with an enzyme from the venom of *N. naja oxiana*.
- The modified factor Va_{NO} lacked a 27-amino acid peptide contained in Va as a result of the incubation.
- Comparative testing was performed using factor Va and the modified factor Va_{NO}.
- The modified factor Va_{NO}, from which was cleaved the 27-amino acid peptide contained in factor Va, exhibited greater prothrombin activation than factor Va.
- Bakker stated "[t]hus, the final 27 carboxyl-terminal residues of the factor Va...did not play a role in the increase of...prothrombin activation," p. 20667.

Thus, as Applicant previously explained, in view of these teachings by Bakker, an artisan, interested in inhibiting thrombin generation, would be motivated to investigate other amino acid regions in factor Va besides those of the 27 amino acid section that were cleaved from factor Va by the snake venom.

The Office also asserted that "Bakker teaches that when the C-terminal 27 amino acids are removed from Factor Va, the resulting peptide (Va_{NO}) activates thrombin more effectively than does native Factor Va."

No! Bakker entirely fails to provide any teaching or even suggestion as to binding thrombin, or how or what region(s) of factor V or fragments thereof, may be responsible for binding to thrombin.

Instead, Bakker investigates binding prothrombin. Thrombin and prothrombin are different from one another. Thrombin is produced by an enzymatic cleavage of two sites on prothrombin by activated factor X. Prothrombin is produced in the liver. Although thrombin is derived from prothrombin, these agents are different from one another and have entirely distinguishable roles and functions in the blood coagulation process.

The Office continued and argued, "the reply appears to stipulate to the fact that Va_{NO} is a less effective thrombin inhibitor than is Factor Va."

No. Applicant is not agreeing to or contending such. Applicant respectfully directs the Office to Bakker's teaching that Va_{NO} exhibited greater prothrombin activation than Va.

It is respectfully submitted that upon further review of this matter, particularly after a detailed review of Bakker, the Office will appreciate that Bakker does in fact teach away from the present invention. After Bakker's pronouncement that "the final 27 carboxyl-terminal residues of the factor Va...did not play a role in the increase of...prothrombin activation," an artisan would be motivated to investigate other regions of factor Va. A pronouncement to investigate other regions most certainly constitutes a teaching away. As a result of such teaching away, the present rejection has been rebutted and should now be withdrawn.

4. References Applied Collectively

Additional arguments by the Office were presented on page 9 of the June 3 Office Action in support of the rejection:

> Applicants urge that none of the references teaches the claimed peptide (Reply, pages 33-34). However, none of the references is applied alone; the references are applied in combination and in view of the state of the art at the time of the invention, and the claimed invention becomes obvious when the references are considered together as a whole rather than each alone.

Applicant has never, nor now, viewed the present rejection as based upon only one of the four cited references. The Office is respectfully requested to review pages 30-52 of Applicant's previously submitted Amendment C dated March 26, 2009. There, Applicant addressed the nature and description of each of the cited references and presented the scope and content of the prior art. There, Applicant also addressed and discussed the differences between the collection of prior art and the claims. Also, there, Applicant addressed and discussed the level of ordinary skill in the art. The four references and in particular their combination, have been addressed and analyzed in great detail. It is unclear why the Office would insinuate that Applicant has only addressed each reference individually.

5. Claims Are Directed to Peptides and Thrombin

The Office also asserted that:

> Applicant alleges that the references do not teach binding between Factor V and thrombin (Reply, pages 34-35), but the examiner submits that the instant claims are drawn to peptides and peptides only. As set forth in the rejection, the prior art provides motivation to identify the portion of Factor V involved in thrombin cleavage and activation (see Pittman and Hortin, both of which establish a link between Factor V sulfation and thrombin activation). Hortin teaches that sulfation of tyrosine residues in other proteins modulates their direct binding to thrombin (see page 946, column 2) and explicitly contemplates a direct interaction of Factor V and thrombin. Again, it is not clear how following the explicit direction provided by the prior art constitutes innovation.

Pages 9-10 of the June 3, 2009 Action.

Certain claims specifically recite peptides. However, most claims of the currently rejected claims also expressly recite thrombin, such as claims 112-115, 120-127, 128-135, and 136-142. Thus, it is not accurate to assert that the claims recite only peptides.

Notwithstanding this matter, Applicant's previous explanation concerning the failure by the cited art to teach direct binding between the claimed peptides and thrombin (see pages 34-35 of Applicant's previously submitted Amendment C dated March 26, 2009) was provided in regards to why the cited art should not be relied upon for the present rejection. As explained in Applicant's previous response, there is absolutely no evidence presented in any of the noted references for direct binding between factor V and thrombin. And, more significantly, none of the cited references teach or describe binding between the claimed peptides and thrombin. None of Pittman, Bakker, and particularly Hortin present any evidence such as data demonstrating such alleged binding. And, furthermore, none of Pittman, Bakker, nor Hortin show that DYDY, DYDYQ, or the sulfonated versions of these sequences are direct binding sites for thrombin.

As previously explained in Applicant's prior Amendment C, a significant feature of the present invention is the discovery of specific amino acid sequences, i.e. DYDY or DYDYQ, that directly bind with thrombin and thus serve as anticoagulants. The present invention provides peptides that consist of these amino acid sequences and which then upon binding to thrombin, inhibit the activation of factor V to thereby inhibit subsequent

thrombin generation. No art has been cited which sufficiently teaches this subject matter.

6. This Field of Art is Unpredictable

In support of the rejection, the Office also argued that:

> Applicant alleges that the art was unpredictable at the time of the invention (Reply, pages 35-37), but the examiner disagrees. Obviousness does not require absolute predictability; however, at least some degree of predictability is required. See M.P.E.P. § 2143.02. Applicant implies that the prior art must have explicitly envisaged the exact invention to be considered "predictable," which is incorrect.

Page 10 of the Office Action.

It is unclear why the Office contends that Applicant urges "that the prior art must have explicitly envisaged the exact invention to be considered 'predictable.'" Applicant has never, nor now, asserted such. The Office is respectfully requested to review pages 36-37 of Applicant's previously submitted Amendment C dated March 26, 2009 for Applicant's explanation of why a skilled artisan in this field of art would not have had a reasonable expectation of success in identifying the claimed sequences of amino acids, and/or identifying the claimed peptides, from the numerous possibilities presented. Furthermore, the Office is respectfully requested to review those pages as to why a skilled artisan would not have had a reasonable expectation of success in identifying the particular sequences which can be utilized in the claimed peptides for direct binding to thrombin, thereby serving as important anticoagulant agents.

7. Objective Evidence

The Office also contended on page 10 of the June 3, 2009 Action that:

> Applicant again alleges the presence of objective evidence of nonobviousness (Reply, pages 37-39), but the examiner maintains that applicant's reply does not clearly indicate what aspects of this data are unexpected; rather, the reply refers to the figures generally. The burden is on applicant to explain data, particularly pointing out that it represents results that are both unexpected and significant. See M.P.E.P. § 716.02(b).

Accompanying this Amendment D is a Declaration by the inventor Dr. Michael Kalafatis in which further detailed explanations are presented concerning the data presented in the present application. This Declaration constitutes additional objective evidence in support of the patentability of the pending claims.

8. Additional Reasons for Withdrawal of the Present Rejection

After presenting select passages from the KSR decision, the Office concluded and argued:

> The gist of KSR is that no explicitly stated motivation for combination need be present in the art for a proper rejection under 35 U.S.C. § 103 if the art fairly suggested the modifications necessary to arrive at the claimed invention.
>
> Nonetheless, the examiner indeed provided a motivation and a showing of reasonable expectation of success for the person of ordinary skill in the art to combine the teachings of the prior art, as detailed above. Applicant has provided no evidence or convincing argument that true innovation led to the claimed invention and that skilled artisans could not have arrived at the claimed composition at the time of the invention, given the advanced state of the art as set forth in the rejection.

Page 11 of the June 3, 2009 Office Action.

It is respectfully submitted that Applicant has in fact, provided a detailed explanation why the present rejection is unsupported and must be withdrawn. The Office is requested to review pages 39-52 of previously filed Amendment C.

The Office carries the burden in supporting a prima facie obviousness rejection. That burden has still not been satisfied. Applicant previously requested the Office to

address the following questions set out in Applicant's previously filed Amendment C. However, all of these were ignored. The Office is again requested to address:

- Regarding the Office's assertion that a skilled artisan would have had a reasonable expectation of success in sulfating either or both of the tyrosine residues at positions 696 and 698 within Factor V, no explanation was provided as to how within the 2200 amino acid sequence of factor V, the tyrosines at positions 696 and/or 698 were arrived at. See pages 39-40 of Applicant's previously filed Amendment C.
- The Office previously contended that a skilled artisan would have been motivated to produce the claimed peptides because Bakker allegedly teaches that the C-terminal portion of factor V heavy chain, which comprises tyrosine residues 696 and 698, is purportedly the domain required to bind prothrombin. However, as previously asked on page 41 of Applicant's prior Amendment C, which agent does the Office consider the portion of factor V heavy chain binding with? Thrombin or prothrombin?
- The Office previously argued that a skilled artisan would have been motivated to determine which of the 27 residues from Bakker is necessary for "the interaction" and which are not. However, as previously pointed out on page 42 of Applicant's previously filed Amendment C, no explanation or basis was provided by the Office for this assertion. No reasons in the form of objective evidence were provided by the Office as to why or how a skilled artisan would have been motivated to determine

which of these 27 residues is necessary for the interaction and which are not. Moreover, the Office did not explain what exactly is meant by its reference to "interaction."

- The Office also asserted that it would have been routine experimentation on the part of a skilled artisan to sulfate the residues, i.e. the 27 amino acid fragment described by Bakker. The Office argued that such would have been routine because allegedly, Pittman teaches methods for doing so. However, the Office did not explain how would a skilled artisan, seeking to identify specific peptides for direct binding to thrombin, have arrived at the Bakker reference and its description of snake venom cleaving off the 27 amino acid sequence? Moreover, the Office never explained how other teachings in Pittman can be ignored such as Pittman's teachings that the "sites of tyrosine sulfation in factor V remain to be elucidated" and "we do not know if efficient thrombin cleavage of the light chain [fragment of factor V] also requires tyrosine sulfation." Furthermore, the Office conveniently ignored and did not address a teaching by Hortin that "[t]he precise sites of sulfation in factor V remain to be established." See pages 42-43 of Applicant's previously filed Amendment C.
- The Office did not identify any specific statements in Hortin to support the Office's conclusion that a skilled artisan would have had a reasonable expectation of success that the claimed peptides would inhibit thrombin activity, see pages 43-44 of Applicant's Amendment C. Instead, Hortin, at

most, speculates that six tyrosines at amino acid locations 696, 698, 1494, 1510, 1515, and 1565 are likely sites of sulfation. The Office did not provide any reasons or evidence why amino acid locations 696 and 698 are to be selected and why locations 1494, 1510, 1515, and 1565 are all to be ignored. In addition, the Office did not provide any evidence as to the significance of these sites. Even if their teaching as sulfation sites may be fairly inferred from the art (which Applicant contests due to the fact that the cited references clearly note that the various locations are merely speculated and that the locations remain to be identified), the cited art still fails to teach the specific peptides consisting of the four or five recited amino acids.

- The Office previously admitted that "Hortin does not teach...the tetrapeptide DYDY or the pentapeptide DYDYQ." Beginning with that premise then, where is any express teaching in the references to Pittman, Bakker, or Ramabhadran to combine them with Hortin? None of those references teach or describe the claimed peptides DYDY or DYDYQ. And so, how are either of these specific sequences obvious? In fact, the Bakker reference as previously explained actually teaches away. For this reason alone, Bakker certainly provides no teaching, suggestion, or motivation for combining with any of the other references.
- The Office repeatedly asserted that the claimed subject matter could have been arrived at by mere routine experimentation. If so, then why has Applicant's discovery never been disclosed prior to the present

application? Applicant previously posed this question on page 52 of its previously filed Amendment C. No explanation was provided by the Office in this regard.

It is respectfully submitted that in view of the foregoing, the Office will appreciate that the present rejection must as a matter of law be withdrawn, and that all pending claims 1-5, 8, 10, 43-49, 51, and 112-142 are in condition for allowance.

C. Conclusion

If there are any additional fees resulting from this communication, please charge same to our Deposit Account No. 18-0160, our Order No. CSU-17999.

Respectfully submitted,

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